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by

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16. ABSTRACT Pesticides represent an important economic commodity and a very broad class of chemicals. Each year massive amounts of pesticides are produced industrially and are used in agriculture and forestry, as well as in and around the home. In the 1969 report of the Secretary's Commission on Pesticides, it was estimated that in the United States alone there were over 900 active pesticidal chemicals available for use in the form of over 60,000 formulations (Mrak, 1969). In 1975, an estimated 1.3 billion pounds of pesticides were used in the United States (Brown, 1978). Survey projections indicate that the worldwide market for pesticides this year will be close to \$10 billion (Anonymous, 1977). Accumulating evidence suggests that pesticides pervade our environment so extensively that the likelihood of accidental exposure in many urban areas is about equal to that in rural farming communities. The U.S. Environmental Protection Agency estimates that each year over 45,000 persons in the U.S. are poisoned by pesticides (Pimentel and Pimentel, 1979), and the World Health Organization estimates that worldwide there are more 500,000 poisonings each year, with mortality in excess of 1% (WHO, 1973). Pesticides are therefore widespread and widely used in our environment and consequently are an important topic in any discussions about environmental quality and public health.		
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Pesticides represent an important economic commodity and a very broad class of chemicals. Each year massive amounts of pesticides are produced industrially and are used in agriculture and forestry, as well as in and around the home. In the 1969 report of the Secretary's Commission on Pesticides, it was estimated that in the United States alone there were over 900 active pesticidal chemicals available for use in the form of over 60,000 formulations (Mrak, 1969). In 1975, an estimated 1.3 billion pounds of pesticides were used in the United States (Brown, 1978). Survey projections indicate that the worldwide market for pesticides this year will be close to \$10 billion (Anonymous, 1977). Accumulating evidence suggests that pesticides pervade our environment so extensively that the likelihood of accidental exposure in many urban areas is about equal to that in rural farming communities. The U.S. Environmental Protection Agency estimates that each year over 45,000 persons in the U.S. are poisoned by pesticides (Pimentel and Pimentel, 1979), and the World Health Organization estimates that worldwide there are more than 500,000 poisonings each year, with mortality in excess of 1% (WHO, 1973). Pesticides are therefore widespread and widely used in our environment and consequently are an

important topic in any discussions about environmental quality and public health.

Pesticides also comprise a very heterogeneous class of chemicals. The term pesticide offers little insight into either the particular type of chemical or the particular species for which it is used. Pesticides can more descriptively be classified as acaricides, avicides, fungicides, herbicides, insecticides, molluscicides, nematocides, rodenticides, etc., although each of these classes may be comprised of several different types of chemicals. This review will concentrate mainly on several of the major classes of insecticide and acaricide.

Studying the behavioral effects of pesticides is important because most pesticides are designed either to adversely affect the nervous system or to disrupt behavior patterns. Examples of the former type are represented by classes such as organophosphates, carbamates and chlorinated hydrocarbons. In the latter type, the term pestistats is sometimes used (e.g., Hollingworth and Murdock, 1980). Examples of pestistats include pheromones, tri-*n*-butyl tin (which is used as a rodent repellent) and 4-acetylpyridine (which is used to repel pigeons from park areas and fields). Pestistatic action is also an important component in the biological activity of formamidines and synthetic pyrethroids (cf., Hollingworth and Lund, 1982).

Organophosphates. Organophosphate pesticides represent a broad class of chemicals that characteristically inhibit cholinesterases in neural and non-neural tissues. Exposure to life-threatening dosages of organophosphates produces profuse salivation, lacrimation, urination, defecation and motor incoordination. Examples of organophosphates include diazinon, fenitrothion, phosphamidon, mevinphos and diisopropyl fluorophosphate (DFP).

Under most circumstances and in several species, acute organophosphate administration decreases rates of schedule-controlled responding, as well as several other types of performance (see Bignami and Gatti, 1967). Mertens et al. (1975) found, for example, that mevinphos (Phosdrin) produced dosage-related decreases in the responding of gerbils under fixed-ratio, differential-rein-

forcement-of-low-rate and random-interval schedules of food reinforcement. In most instances, decreases in response rates were associated with grossly observable signs of exposure (salivation, tremor, incoordination). Decreases in random-interval reinforced responding were also produced by mevinphos in pigeons and in squirrel monkeys (Lewis et al., 1973; Mertens et al., 1976). An additional experiment by Mertens et al. (1974) found that mevinphos decreased the response rates and increased the number of shocks received by gerbils performing under a free-operant schedule of shock avoidance, but only at a dosage that produced grossly observable signs of exposure.

Decreases in fixed-ratio and fixed-interval reinforced responding have been produced by DFP and parathion in rats, pigeons, hens and rhesus monkeys (Ford and Rosenblum, 1979; Gross-Selbeck, 1978; McMillan et al., 1975; McMillan, 1982; Russell et al., 1975). In the experiments by Ford and Rosenblum (1979), for example, DFP produced dosage-related decreases in the rates at which hens and pigeons performed under a multiple fixed-interval 3-min fixed-ratio 30-response schedule of grain reinforcement. Some of these data are shown in Figure 1 (left and center panels) for the performance of hens. Decreases in response rate appeared equivalent under both components, even though the schedules maintained different rates (about 5 to 1) under control conditions. Similar results were obtained in an experiment by McMillan et al. (1975; cited by McMillan, 1982), in which parathion (0.56 mg/kg) produced proportionately equivalent decreases in the rates at which pigeons responded under a multiple fixed-interval 5-min fixed-ratio 30-response schedule of grain reinforcement.

The right-most panel of Figure 1 illustrates an additional characteristic effect of organophosphates. Performance under fixed-interval schedules is patterned in time (e.g., Kelleher and Morse, 1968), and the pattern can be quantified in several different ways (e.g., Gollub, 1964). In this instance, the percentage of responses during the last minute of the 3-min fixed-interval is plotted. If responding were evenly distributed throughout the interval, baseline values would equal 33%; the much higher baseline values indicate that patterning was prominent. Comparison of the center and right-most panels shows that substantial decreases in overall responding occurred following DFP without appreciable disruption of the temporal

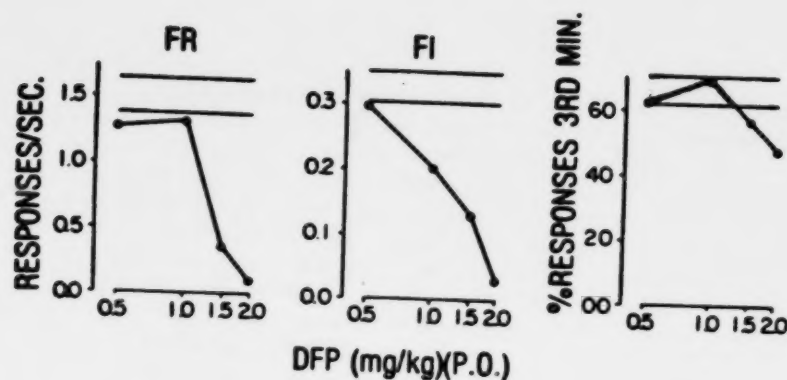


Figure 1. Effects of DFP on the schedule-controlled performance of hens. Hens were trained to perform under a multiple fixed-interval (FI) fixed-ratio (FR) schedule of reinforcement. Shaded areas in the left and center panels represent the range of control response rates following administration of vehicle (corn oil). The shaded area in the right panel represents the range of responses occurring in the last third of the fixed interval, expressed as a percentage of total responses, following vehicle administration. Constant responding throughout the fixed interval would result in a value of 33.3%. Each symbol represents the mean effect of DFP for three hens. Taken from Ford and Rosenblum (1979).

pattern of responding. Similarly, McMillan et al. (1975) found that a dosage of parathion producing greater than a 50% decrease in overall fixed-interval responding did not disrupt the temporal pattern of responding within the interval (McMillan, 1982).

Collectively, then, the above data indicate that acute organophosphate exposure decreases rates of responding under several schedules of reinforcement, and does not appreciably disrupt the temporal pattern of responding maintained under fixed-interval schedules. Under many circumstances, decreases in response rates are accompanied by grossly observable signs of exposure (see also Clark, 1971).

Several experiments have also determined the effects of repeated administration of organophosphates. Under most conditions, tolerance develops to the behaviorally

disruptive effects with repeated exposure (e.g., Russell et al., 1969; Overstreet et al., 1974; Russell et al., 1975; McMillan et al., 1975; Giardini et al., 1981; 1982). The available evidence indicates that tolerance development is not heavily dependent on the schedule under which performance is maintained (see McMillan, 1982), or on many other factors in the test environment (Giardini et al., 1981; see also Russell, 1971).

Carbamates. Carbamate pesticides represent another broad class of chemicals that, like organophosphates, inhibit cholinesterases but in contradistinction do so in a reversible manner. Exposure to life-threatening dosages produces effects similar to those of the organophosphates. Examples of carbamates include aldicarb, carbaryl and propoxur, as well as the nonpesticidal carbamates physostigmine, pyridostigmine and neostigmine.

The acute effects of carbamates on schedule-controlled behavior closely resemble those produced by organophosphates. That is, under most circumstances carbamates produce dosage-related decreases in schedule-controlled responding (see also Bignami and Gatti, 1967). Anger and Wilson (1980), for example, reported that carbaryl produced dosage-related decreases in the response rates of rats under a variable-interval 5-min schedule of food reinforcement. Carbaryl also produced decreases in responding under a fixed-ratio schedule (Sideroff and Santolucito, 1972) and under multiple variable-ratio extinction (Goldberg and Johnson, 1964). Disruptions in operant performance were generally accompanied by grossly observable signs of exposure.

The effects of carbamates on the temporal pattern of responding resemble the effects described above for organophosphates. In an experiment by Vaillant (1964), for example, appropriate dosages of both physostigmine and neostigmine completely suppressed the performance of pigeons under a multiple fixed-interval 5-minute fixed-ratio 30-response schedule of grain reinforcement. Once responding began to recover, however, performance during the fixed-interval component retained its characteristic within-interval pattern. This effect is shown for one pigeon in Figure 2. A similar effect was obtained in mice following both physostigmine and neostigmine (Wenger, 1979). Wenger (1979) and Vaillant (1964) also found that, as with the organophosphates, the decreases in overall rates of

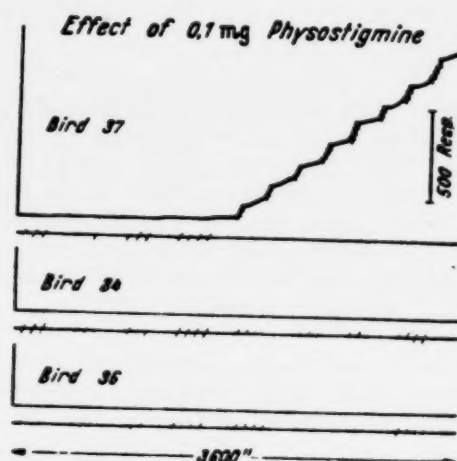


Figure 2. Cumulative response records of the effect of physostigmine on the schedule-controlled performance of pigeons. Pigeons were trained to perform under a multiple fixed-interval fixed-ratio schedule of reinforcement. Physostigmine completely suppressed responding for the entire session for two pigeons. For the third pigeon (Bird 37) response suppression was quickly followed by a return to a near-normal pattern of responding. A similar rapid recovery of performance was reportedly seen when the session duration was extended for the other two pigeons. Taken from Vaillant (1964).

responding under multiple fixed-interval fixed-ratio schedules were proportionately equivalent for the two components. Taken together, these data indicate that carbamates produce dosage-related decreases in rates of responding that do not appear to be schedule specific. Decreases in fixed-interval responding are ordinarily not accompanied by disruption of the within-interval pattern of responding. Disruptions in responding following large dosages are ordinarily associated with grossly observable signs of exposure. The acute effects of carbamates, therefore, are very similar to those of the organophosphates.

Organochlorines. Organochlorine pesticides are chlorinated hydrocarbons that have been used widely in agriculture and in the control of disease-bearing insects. Exposure of rats to life-threatening dosages produces twitching of the ears and vibrissae, hyperthermia,

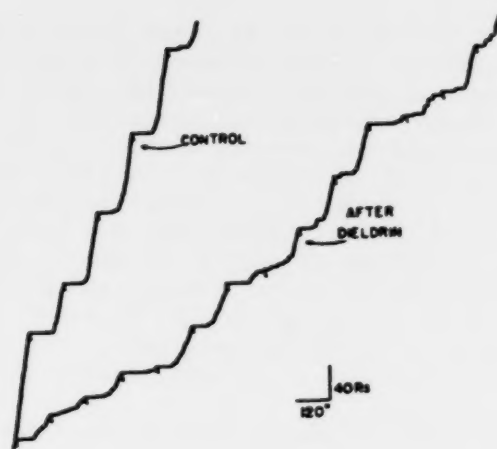


Figure 3. Cumulative response records of the effects of dieldrin on the schedule-controlled performance of a Japanese quail. The left record represents control performance under a fixed-interval 120-sec schedule of reinforcement. The right panel represents performance following 5.0 mg/kg dieldrin. Note that dieldrin decreased overall response rate and disrupted the temporal pattern of responding. Taken from Burt (1975).

hyperreactivity to stimuli, fine and coarse tremor, and convulsions. Examples of chlorinated hydrocarbon pesticides include DDT, lindane, dieldrin, endrin, endosulfan, mirex and chlordane. Although they were once used widely, concern over persistence in the environment, concentration in the food chain, and high cumulative toxicity has restricted the use of many of these pesticides in the U.S. in recent years.

There are very little data available on the acute effects of organochlorines on schedule-controlled behavior. Burt (1975) presented some data on the effects of dieldrin on the performance of rats and Japanese quail maintained under fixed-interval schedules of food reinforcement. Dieldrin decreased overall rates of fixed-interval responding and disrupted the within-interval pattern of responding in both species. The effect of dieldrin on the performance of one quail is shown in Figure 3. Burt (1975) noted that the

effects of dieldrin persisted for at least two days in rats and five days in quail following acute administration. Moreover, the dosages of dieldrin producing behavioral effects were reportedly a substantial percentage of the LD-50. Similar results were recently obtained in my laboratory with the cyclodiene derivative endosulfan. Rats were trained to perform under a fixed-interval 120-sec schedule of milk reinforcement. Endosulfan was then administered p.o. at dosages of 2.5, 5, 10 and 20 mg/kg. Substantial decreases in overall responding and disruptions of the within-interval pattern of responding occurred only at the largest dosage. In another experiment, the LD-50 for endosulfan was determined to be approximately 27 mg/kg.

Dietz and McMillan (1979a,b) compared the effects of daily administration of mirex and chlordecone on the performance of rats under several schedules of reinforcement, including a multiple fixed-interval 2-min fixed-ratio 12-response schedule. Both pesticides produced delayed disruptions in performance, with the delay being inversely proportional to the dosage administered daily. Dietz and McMillan (1979a) reported that the disruptions often occurred before the appearance of grossly observable signs of exposure (most notably tremors). In many instances, however, death occurred with daily dosing. Moreover, there was no clear evidence of a differential disruption in performance under the two components of the multiple schedule, and no mention of whether these pesticides disrupted the temporal pattern of responding within the fixed-interval component. Dietz and McMillan did, however, provide evidence suggesting that the effects of mirex and chlordecone depended on baseline characteristics of performance prior to dosing. Collapsing across all schedule conditions, an approximate inverse relationship was noted between baseline response rates maintained under the different schedules and the direction of effects produced by both pesticides.

In summary, the scant data available suggest that certain organochlorine pesticides may disrupt performance differentially under some schedule conditions and disrupt the temporal pattern of responding maintained by fixed-interval schedules. These effects are generally produced by dosages that are a substantial proportion of the LD-50 and that are accompanied by grossly observable signs of exposure.

Pyrethroids. Pyrethroids are pesticides that were originally derived from pyrethrum extracted from the chrysanthemum flower. Many synthetic pyrethroids have been recently developed that are many times more potent than natural pyrethroids and that have a relatively high selectivity of pesticidal action (i.e., injurious to insects and other pests but not to mammals and other non-target species). As a consequence, use of synthetic pyrethroid pesticides is currently growing world-wide. Exposure of rats to life-threatening dosages results in one of two types of syndromes, depending on the particular pyrethroid (Verschoyle and Aldridge, 1980). Deltamethrin and fenvalerate, for example, produce a syndrome of coarse whole-body tremor that progresses to sinuous writhing (choreoathetosis) accompanied by profuse salivation. Cismethrin and permethrin, on the other hand, produce aggressive sparring behavior and hyperreactivity that progresses to prostration accompanied by coarse whole-body tremor.

Very little data are available on the effects of synthetic pyrethroids on schedule-controlled behavior. Bloom et al. (1983) obtained dosage-related decreases with technical-grade permethrin in rats responding under a variable-interval 20-sec schedule of food reinforcement. Additional experiments showed that the decreases produced by technical-grade permethrin were due largely to the cis-isomer, and that a single dosage of deltamethrin also decreased responding. Dosage-related decreases in fixed-interval and fixed-ratio reinforced responding have been obtained (MacPhail et al., 1981; Leander and MacPhail, unpublished; MacPhail, unpublished; Glowa, 1984). In the experiment of Leander and MacPhail, deltamethrin tended to decrease the responding of pigeons under the fixed-interval component more than under the fixed-ratio component of a multiple schedule. In addition, deltamethrin did not appreciably disrupt the pattern of responding within the fixed-interval component. Glowa (1984) reported that deltamethrin decreased overall rates and disrupted the temporal pattern of responding of mice under a fixed-interval 60-sec schedule of milk reinforcement, but only at dosages that substantially decreased overall response rates. In a recent experiment from my laboratory, deltamethrin produced dosage-related (1-8 mg/kg) decreases in the response rates of rats under a fixed-interval 180-sec schedule of milk reinforcement, and disrupted the temporal pattern of responding within the interval, but only at the largest

dosage, which produced a substantial decrease in overall responding. Deltamethrin-induced disruptions of schedule-controlled behavior generally occur at dosages that do not produce grossly observable signs of exposure.

Formamidines. Formamidines comprise another relatively new class of pesticide that has proven to be highly effective in controlling certain types of mites and ticks. Their toxicity in mammalian species is generally considered to be low, but because of reports of the carcinogenic potential of certain breakdown products their use in this country is relatively restricted at this time. Exposure to life-threatening dosages produces hyperreactivity and convulsions. Examples of formamidine pesticides include chlordimeform, amitraz and their active metabolites norchlordimeform and BTS-27271 (U-40481A). Most of what is known about the formamidines stems from experiments on chlordimeform, which is widely considered to be the prototype of this class.

In general, chlordimeform produces dosage-related decreases in overall rates of responding under fixed-ratio and fixed-interval schedules of reinforcement (Glowa, 1984; Leander and MacPhail, 1980; MacPhail and Leander, 1981; Peele et al., 1984). In an experiment by MacPhail and Leander (1981), for example, chlordimeform produced dosage-related decreases in the rates at which rats responded under fixed-ratio schedules of milk reinforcement (FR 10, FR 40). Slightly greater effects were obtained on fixed-ratio-10 performance, and under both schedules the decreases in overall responding were due to both increases in the pause following reinforcement and decreases in the rate of responding once it was initiated. Figure 4 shows the effect of chlordimeform on the performance of pigeons under a multiple fixed-interval 5-min fixed-ratio 30-response schedule of grain reinforcement (Leander and MacPhail, 1980). Chlordimeform generally decreased responding under the fixed-interval component in a dosage-related fashion. Increases in responding under the fixed-ratio component were evident at certain dosages in three of the four pigeons; larger dosages, however, decreased fixed-ratio-reinforced responding. Moreover, for all four pigeons certain dosages of chlordimeform preferentially decreased fixed-interval reinforced responding. Chlordimeform also disrupted the temporal pattern of responding maintained within the fixed-interval component, as shown in Figure 5.

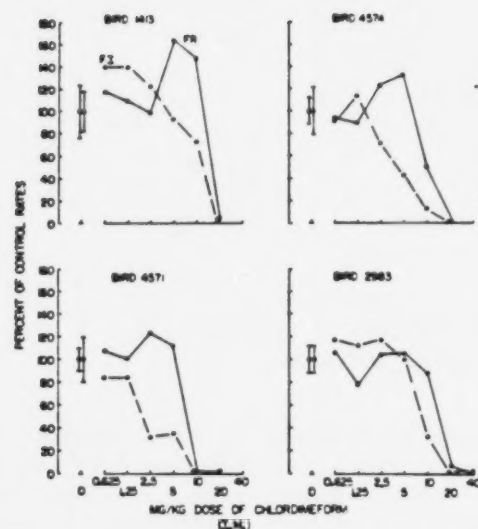


Figure 4. Effects of chlordimeform on the schedule-controlled performance of pigeons. Pigeons were trained to perform under a multiple fixed-interval (FI) fixed-ratio (FR) schedule of reinforcement. Points and brackets above 0 indicate mean $\pm$ SD control performance. Each remaining symbol represents the mean effect of at least two administrations of chlordimeform. Taken from Leander and MacPhail (1980).

Here, response patterning was quantified by the quarter-life statistic. Decreases in quarter life with increasing dosage were associated with increases in responding early in the fixed interval and decreases in responding later in the fixed interval. Similar rate-dependent effects of chlordimeform were recently obtained in rats (Peele et al., 1984).

In summary, chlordimeform generally decreases rates of responding under several schedules. In the case of pigeons, at least, the decreases in fixed-interval responding occur at smaller dosages than do decreases in fixed-ratio responding. In addition, under many circumstances chlordimeform disrupts the temporal pattern of fixed-interval responding by increasing responding early in the interval and

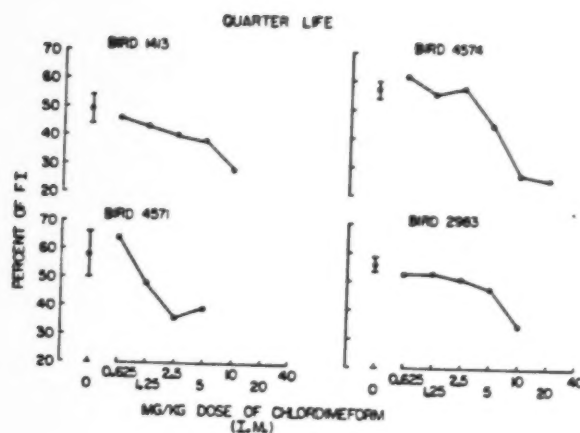


Figure 5. Effects of chlordimeform on the schedule-controlled performance of pigeons. Data are for the same pigeons as in Figure 4 and represent the effects of chlordimeform on the temporal pattern of responding within the fixed-interval component. Quarter life represents the amount of time (expressed as a percentage of the fixed-interval) required to emit 25% of the total responses; a value of 25% represents a constant rate of responding whereas greater values indicate positively accelerated responding throughout the fixed interval. Points and brackets above 0 indicate mean $\pm$ SD control performance. Each remaining symbol represents the mean effect of at least two administrations of chlordimeform. Taken from Leander and MacPhail (1980).

decreasing responding later in the interval (i.e., the effects are rate dependent). Finally, decreases in operant behavior produced by chlordimeform generally occur in the absence of grossly observable signs of exposure.

Conclusions. There are relatively little data available as of yet on the effects of pesticides on schedule-controlled behavior. Data that are available are largely fragmentary, owing to differences in species, in the schedules and events maintaining responding, and in the particular pesticide chosen for study. Future experiments should focus on systematically determining the effects of pesticides, including additional pesticide classes as well as additional chemicals within each class, and the environmental conditions under which pesticide effects can

be modified. Nevertheless, based on the results reviewed above, certain generalizations can be tentatively put forth. Carbamates and organophosphates generally produce non-schedule-dependent reductions in rates of responding and do not appreciably disrupt the pattern of responding maintained under fixed-interval schedules. Decreases in schedule-controlled responding are often accompanied by grossly observable signs of exposure. Organochlorine pesticides may produce schedule-dependent effects, and ordinarily they do disrupt the temporal pattern of fixed-interval responding, but these effects typically occur at dosages that are a substantial proportion of the LD-50 and which are likely to produce grossly observable signs of exposure. Pyrethroids generally disrupt schedule-controlled responding in a non-schedule-dependent manner, and may or may not disrupt the temporal pattern of responding under fixed-interval schedules. The disruption of the fixed-interval pattern of responding generally occurs at dosages that produce substantial decreases in the overall rate of responding. Pyrethroid effects are generally obtained in the absence of grossly observable signs of exposure. Formamidines, or more precisely chlordimeform, produces schedule-dependent effects on overall rates of responding and markedly disrupts the temporal pattern of responding under fixed-interval schedules. Chlordimeform's effects are ordinarily obtained at dosages that do not produce gross signs of exposure.

Schedule-dependencies and rate-dependencies in the effects of certain pesticides are evidence that environmental conditions can be important determinants of the behavioral effects of pesticides. In behavioral pharmacology similar dependencies are often, but not always, obtained. It is simply too early to tell whether such dependencies will be equally pervasive in behavioral toxicology. Schedule- and rate-dependencies are, however, only two manifestations of what Sidman (1956) called drug-behavior interactions. Drug-behavior interactions abound in behavioral pharmacology (e.g., Kelleher and Morse, 1968). Considerable additional research will be required in order to assess the extent to which drug-behavior interactions occur in behavioral toxicology. It may be that drug-behavior interactions do not figure prominently in the effects of organophosphate and carbamate pesticides but are important factors in the effects of organochlorine and formamidine pesticides.

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